MECHANISMS OF MYOCARDIAL ISCHEMIA

Part of "46 - Coronary Blood Flow and Myocardial Ischemia"

Myocardial ischemia develops when coronary blood flow becomes inadequate to meet the requirements of the myocardium for oxygen and metabolic substrates to maintain adequate cardiac function. Myocardial ischemia can result from (1) an increase of myocardial workload, and hence oxygen demand, in the presence of a flow-limiting coronary artery stenosis or (2) a reduction of coronary blood flow caused by epicardial or microvascular coronary artery constriction or by acute thrombosis. These mechanisms may act in combination in some patients as well as in different ischemic episodes in a same patient (Fig. 46-5).50

FIGURE 46-5 Pathophysiologic components of myocardial ischemia. The different clinical ischemic syndromes may result from fixed obstruction to coronary blood flow caused by atherosclerotic plaques, from coronary vasoconstriction of epicardial or of microvascular vessels, and from coronary thrombosis. (Modified from Maseri A, Crea F, Lanza GA: Coronary vasoconstriction: Where do we stand in 1999. An important, multifaceted but elusive role. *Cardiologia* 1999;44:115. With permission.)

In clinical practice, coronary stenoses are often considered the only or main cause of myocardial ischemia because they are the most obvious and readily plausible culprit. Acute thrombosis can be recognized only until thrombi are lysed or become incorporated into the atherosclerotic plaques. The detection of coronary spasm and of dynamic stenosis is even more elusive, because they are very transient and usually require repetition of angiography following nitrates or provocative tests. Finally, microvascular constriction may be inferred only indirectly by slow distal progression of the flow of dye at angiography or by special diagnostic studies.

The clinical presentation of anginal syndromes can provide useful clues as to the role of these distinct pathogenetic mechanisms in precipitating myocardial ischemia.

Flow-Limiting Stenosis

EFFECTS OF FLOW-LIMITING STENOSIS ON BLOOD FLOW

The presence of epicardial coronary artery stenosis, caused by atherosclerotic plaques, is by far the most frequent

angiographic finding in any cardiac ischemic syndrome. However, a stenosis becomes flow-limiting only when it determines a measurable transstenotic pressure gradient at rest. The transstenotic pressure gradient increases with increases in flow, more than doubling when blood flow doubles.

A basal gradient at rest may not cause myocardial ischemia, as flow is maintained by compensatory distal arteriolar dilatation. This, however results in a local reduction of

coronary flow reserve. The greater the basal transstenotic pressure gradient, the greater the reduction of coronary flow reserve and the lower the level of cardiac work at which myocardial ischemia appears during effort (*ischemic threshold*). Experimental studies in dogs have shown that the acute reduction of coronary diameter by >50 percent causes a measurable basal transstenotic pressure gradient.51 Further decreases in diameter cause an exponential increase of transstenotic pressure gradient and a reduction of maximal coronary blood flow (Fig. 46-6). A sudden 85 to 90 percent reduction in diameter of an epicardial coronary artery is required to cause myocardial ischemia at rest. The decrease in poststenotic pressure may be reduced by the gradual development of collateral blood flow (see below).

FIGURE 46-6 Schematic illustration of the relationship between coronary blood flow and the transstenotic pressure gradient. This relationship becomes curvilinear because of energy losses caused by blood flow turbulence across the stenosis (*solid lines*). Poststenotic pressure decreases progressively with the increase of stenosis severity and, for a given stenosis, it decreases markedly with increasing flow. In the absence of collateral flow, a stenosis 80 percent in diameter causes a drop in poststenotic pressure of about 12 mmHg, which would increase to about 30 mmHg when flow doubles. (Modified from Gallagher et al.170 With permission.)

The general relationship between the severity of coronary stenosis, as assessed on coronary angiography, and impairment of coronary flow reserve has been confirmed in patients.52,53 However, angiographic judgment of the hemodynamic consequences of coronary stenoses is difficult because (1) quantitative angiography does not permit an accurate three-dimensional measure of stenosis; (2) the luminal reduction is estimated with reference to the coronary segment proximal to the stenosis, which may be restricted by atheroma or, conversely, enlarged because of vascular remodeling; (3) the stenotic resistance is linearly related to the length of the stenosis and the flow turbulence caused by stenotic irregularities.

Several invasive and noninvasive methods have been proposed to assess the hemodynamic significance of coronary stenosis.54 The measurement of fractional flow reserve (FFR) has been suggested as one of the most reliable of these.55 FFR is calculated as the ratio between the mean pressures distal and proximal to the stenosis during maximal vasodilatation, usually obtained by intracoronary adenosine.* A FFR <0.75 is usually believed to indicate that the stenosis is capable of causing myocardial ischemia. However, the assessment of coronary stenoses can also more easily be done—after intracoronary nitrates have been administered to eliminate the possible vasomotor component of the stenosis—by direct measurement of the basal transstenotic pressure gradient. Indeed, in the absence of a measurable basal gradient, the development of ischemia, at rest or even during effort, should not be attributed to the hemodynamic effect of the stenosis.

DYNAMIC MODULATION OF CORONARY STENOSES

Coronary flow-limiting stenoses are caused by concentric or eccentric atherosclerotic plaques with or without the potential for local vasomotor changes. Fixed flow-limiting stenoses present as smooth muscle cell atrophy and/or plaque rigidity and are associated

with a predictable ischemic threshold during physical effort. Dynamic stenoses are usually eccentric, with compliant segments of the wall and preserved muscular media, and are associated with a variable ischemic threshold. The vasomotor potential of coronary stenoses can also be assessed directly at angiography by intracoronary infusion of vasodilator and/or vasoconstrictor substances.56,57 Vasoconstriction at the site of stenosis may result from increased release of neural or local vasoconstrictor stimuli, impaired vasodilator mechanisms, abnormal response of dysfunctional vascular smooth muscle cells to vasoactive stimuli, or a variable combination of these mechanisms. For example, exercise and cold pressor testing cause vasodilatation in normal vessels but vasoconstriction at the site of stenosis.58,59 Vasoconstrictor autacoids, produced locally by the endothelium (endothelin),60,61 in the adventitia (histamine, leukotrienes), or released by activated platelets (thromboxane A_2, serotonin) are also powerful potential constrictor stimuli. Defective production and/or release of vasodilator substances (in particular EDRF) may increase basal coronary tone and prevent flow-mediated arterial vasodilatation during increased M[V with dot above]o_2. 62,63 and 64 In animal models and possibly also in unstable patients, the severity of the stenosis may be modulated by the transient deposition of platelet aggregates.

CORONARY COLLATERAL CIRCULATION

The drop in poststenotic pressure caused by flow-limiting stenoses stimulates the development of collateral circulation from other coronary artery beds. The blood flow from collateral vessels increases poststenotic pressure, thus improving coronary flow reserve.

Collateral vessels develop from the progressive enlargement of preexisting intercoronary arterial anastomoses. These vary greatly in number among mammalian species, being more numerous in guinea pigs and dogs, less so in pigs and rats, and practically absent in rabbits and sheep. Blood flow through these anastomoses begins, as a consequence of the flow-limiting stenosis, when a pressure gradient develops between their origin and termination.50

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Preexisting anastomoses are progressively transformed into mature collaterals over a period of 3 to 6 months by initial widening and remodeling, subsequent proliferation of endothelial and smooth muscle cells, and the development of a smooth muscle coat, leading to vessels with a final diameter of 20 to 200 μm. Collateral blood flow may also develop by the formation of new vessels, but in the dog this mechanism contributes less than 5 percent of total collateral flow.50

Blood flow through collaterals is determined by the driving pressure and the vessels' resistance, which is influenced by neural and humoral stimuli and by local vasoactive autacoids.65,66,67 and 68

In patients with flow-limiting stenoses, the number and size of collateral vessels is quite variable. At one extreme, some patients with an occluded coronary artery do not have signs of ischemia because the collateral circulation provides an adequate blood supply to the territory of the occluded coronary branch. At the other extreme, some patients with severe flow-limiting coronary stenosis do not show detectable improvement of their ischemic

threshold over time; when the vessel occludes, they develop myocardial infarction. These individual differences in coronary collateral circulation are probably due to genetic factors.69

In experimental animals, no intervention was convincingly shown to improve the development of collateral vessels. In patients, heparin70 and fibroblastic growth factor-1 (FGF-1)71,72 have been suggested to promote collateral growth, but the data are not yet definitive. Recent observations have demonstrated a role for insulin in regulating the gene expression for VEGF and its receptors in microvascular and cardiac tissue.73

CORONARY STEAL DISTAL TO FLOW-LIMITING STENOSIS

In the presence of flow-limiting stenosis, myocardial ischemia may develop as a result of a diversion of blood flow from a myocardial region with a very severe impairment of coronary flow reserve—determining an almost maximal arteriolar dilatation in basal conditions—to a myocardial region with sufficiently preserved coronary flow reserve.

Such a coronary diversion may occur (1) from the subendocardium, as a result of vasodilatation of subepicardial vessels, which increases subepicardial flow but causes a further critical decline in poststenotic pressure (*transmural coronary steal*),50,74 or (2) from collateralized territories when the coronary artery supplying the collaterals also presents a flow-limiting stenosis proximal to their origin. In the latter case, arteriolar dilatation in the territory of the stenosed parent artery causes increased flow but a further drop in perfusion pressure at the origin of collaterals, which reduces collateral flow (*lateral coronary steal*).75 In both instances the vasodilatation responsible for the steal can be induced by vasodilator drugs or an increase in M[V with dot above]o_2.

Coronary Artery Spasm

Coronary artery spasm is the pathogenetic mechanism of variant angina, but it can play a role in some patients who present with acute coronary syndromes.

CORONARY SPASM IN VARIANT ANGINA

In patients who present with a variant form of angina (see below), myocardial ischemia is caused by an occlusive epicardial coronary spasm.50 Spasm may develop at the site of subcritical or critical stenosis as well as in angiographically normal coronary arteries. Occlusive spasm usually causes transmural ischemia with ST-segment elevation. In some cases, however, spasm is subocclusive and causes subendocardial ischemia with ST-segment depression.76

In patients with variant angina, spasm tends to recur in the same arterial segment and can be precipitated by sympathetic and parasympathetic stimuli and by a variety of triggers—such as ergonovine, histamine, dopamine, acetylcholine, and serotonin—acting on different receptors as well as by an increase in arterial pH to 7.65 or 7.70.77,78,79,80,81 and 82 Collectively, these findings suggest a hyperreactivity of local smooth muscle to a wide variety of constrictor stimuli. This may be caused by a variety of postreceptorial intracellular abnormalities.50,65 Some cellular mechanisms potentially able to contribute to the induction of coronary spasm have recently been described; these include increased

rho-kinase activity,83 ATP-sensitive membrane potassium channels,84 and membrane sodium-hydrogen countertransport.85

The postmortem findings at the site of coronary spasm are not specific, but fibromuscular hyperplasia was observed in some cases. The animal model of coronary spasm developed in minipigs,86 on the other hand, is unlikely to adequately reflect the mechanisms of vasospastic angina occurring in patients.

CORONARY SPASM IN ACUTE CORONARY SYNDROMES

Although occlusive spasm is typically observed in patients with variant angina, it may also represent a pathogenetic component of other, more common acute coronary syndromes, including unstable angina,87 unheralded myocardial infarction,88,89 resuscitated sudden cardiac death,90 and post–coronary bypass graft angina.91 In fact, there appears to be a higher prevalence of coronary spasm in patients with acute coronary syndromes (20 to 38 percent) than in those with stable angina (<6 percent).50 Coronary spasm has been found to occur more frequently in Asian than in Caucasian patients with a recent acute myocardial infarction89 (Fig. 46-7).

FIGURE 46-7 Induction of coronary spasm by intracoronary acetylcholine injection in infarct-related arteries (IRAs) and non-infarct-related arteries (NIRAs) of Japanese (J) and Italian (C) patients with recent acute myocardial infarctions. Japanese patients had about a threefold higher prevalence of spastic response in both IRAs and NIRAs. The spastic response was more frequent in IRAs than in NIRAs in Japanese but not in Italian Caucasian patients. (Modified from Pristipino et al.89 With permission.)

The differences in clinical presentation between variant angina and other ischemic syndromes suggest possible different underlying pathogenetic mechanisms. In the case of unstable plaques, the degree of constriction produced by thromboxane A_2, serotonin, and thrombin can be amplified at the site of fresh mural thrombi; in some patients, a local smooth muscle coronary hyperreactivity may contribute to the transition from a nonocclusive platelet-fibrin mural thrombus to an occlusive red thrombus.50

Small Coronary Vessel Dysfunction

The possibility that an impairment of coronary blood flow might occur at the level of distal rather than proximal coronary vessels has received little consideration until recently, as epicardial coronary artery stenoses, spasm, and thrombosis seemed to provide readily available, plausible mechanisms for ischemia. However, several animal and clinical studies have indicated that ischemia can also be caused by the constriction of small coronary vessels.92,93

PHARMACOLOGIC STUDIES IN HUMANS

In patients with angiographically normal coronary arteries, the intracoronary infusion of neuropeptide Y and of high doses of acetylcholine were found to induce myocardial

ischemia without any change in the large epicardial vessels but with extremely slow progression of dye or diffuse constriction of distal branches, respectively, indicating microvascular constriction.50,94 Furthermore, in patients with coronary stenosis, the intracoronary infusion of serotonin caused myocardial ischemia with only small changes in the size of the stenotic lumen but with diffuse constriction of distal branches and reduced filling of collateral vessels.50,94

CLINICAL CLUES TO MICROVASCULAR DYSFUNCTION

In some patients in whom myocardial ischemic episodes cannot be blamed on fixed or dynamic epicardial coronary stenosis, constriction of small coronary vessels may account for the development of myocardial ischemia. Patients with occlusion of a single epicardial coronary artery and no other stenosis may present very wide variations in the ischemic threshold during daily life and exercise testing, which cannot be attributed to dynamic modulation of the stenosis or spasm and are most likely caused by vasomotor changes in small, distal coronary vessels.95

Patients with single-vessel disease following successful coronary angioplasty (PTCA) may continue to present with angina, ST-segment depression on exercise testing, and perfusion defects on stress myocardial scintigraphy96; in such patients a dysfunction of small coronary vessels has been confirmed by intracoronary Doppler blood flow measurements and myocardial positron emission tomography (PET) following administration of vasodilator stimuli.97,98 Microvascular dysfunction is most likely responsible for the reduced coronary dilator response of nonstenosed coronary arteries in patients with coronary disease99,100 and also in those with risk factors but no flow-limiting coronary stenoses.101,102

Patients with syndrome X, who present angina pectoris, positive exercise testing, but angiographically normal coronary arteries and no evidence of epicardial spasm,103 may suffer from some form of microvascular dysfunction. Such a possibility is suggested by stress-induced myocardial perfusion defects on radionuclide studies,104,105 by transient ischemic ST-segment changes during effort testing, and by the reproduction of typical anginal pain, with or without ST-segment ischemic changes, on dipyridamole testing.

An ischemic origin of this syndrome is widely questioned because in the vast majority of studies, no myocardial lactate production or left ventricular dysfunction can be detected during angina and transient ischemic ST-segment changes.106,107 This apparent paradox may be explained by a patchily distributed coronary microvascular dysfunction that is causing dispersed small foci of ischemia. A patchily distributed small vessel constriction may not cause detectable contractile abnormalities or lactate production but produce electrocardiographic (ECG) changes and myocardial perfusion defects when sufficiently confluent.50,94 Observations in animal models, in which ischemia was caused by impairing coronary microcirculation with microspheres50 or endothelin-1 infusion,108 support this concept.

Recent data in syndrome X patients showing intracardiac production of lipid peroxidation products109 following atrial pacing, stress-induced metabolic evidence of myocardial ischemia by phosphorous nuclear magnetic resonance, and an abnormal flow response to adenosine on nuclear magnetic resonance strongly support the microvascular ischemic

origin of this syndrome.110,111,112 and 113

SITE OF MICROVASCULAR DYSFUNCTION

Theoretically, myocardial ischemia caused by microvascular dysfunction may result from abnormal constriction or failure of adequate dilatation of arteriolar or prearteriolar vessels. Arteriolar constriction as a cause of myocardial ischemia would require constrictor stimuli sufficiently strong to overcome the dilator effect of ischemic metabolites on the arterioles themselves.50,94 The constriction of prearteriolar vessels appears a more likely cause of the microvascular alterations responsible for myocardial ischemia. An increased patchy distribution of prearteriolar vasoconstriction has been proposed as a causal mechanism of syndrome X50,94 (Fig. 46-8).

FIGURE 46-8 Model of patchily distributed prearteriolar vasoconstriction in syndrome X. Such a constriction may be present in basal conditions (b1,c1,c2) (*left panel*). As flow increases during metabolic or pharmacologic arteriolar dilation, the pressure drop through constricted prearterioles increases and perfusion pressure at the origin of distal arterioles decreases, thus resulting in small focal areas of myocardial ischemia (*right panel*). Blood flow steal may also occur from the territory supplied by the most constricted prearterioles toward regions supplied by less constricted prearteriolar vessels (c1,c2). At the ends of severely constricted prearterioles, distending pressure may become lower than the critical closing pressure, thus resulting in prearteriolar occlusion (b1). Compensatory myocardial release of adenosine in response to blood flow reduction distal to constricted prearterioles may be sufficient to maintain adequate flow, thus avoiding ischemia, but it may cause angina, particularly when it is associated with enhanced pain sensitivity. (Modified from Maseri A, Crea F, Kaski JC, et al. Mechanisms of angina pectoris in syndrome X. *J Am Coll Cardiol* 1991;17:499. With permission)

MECHANISMS OF MICROVASCULAR DYSFUNCTION

In patients with coronary stenoses, small coronary vessel dysfunction is commonly attributed to atherosclerosis, although it may also be related to neurohumoral stimuli114 or vascular abnormalities (e.g., perivascular fibrosis, medial hypertrophy) associated with systemic diseases, such as hypertension or diabetes.115,116 Small vessel dysfunction in these patients is also frequently attributed to EDRF deficiency on the basis of an abnormal vasomotor response to acetylcholine, but a reduced vasodilator response or a vasoconstrictor response to acetylcholine117,118 could also be caused by an increased constrictor effect of the drug on smooth muscle cells.

In patients with syndrome X, the mechanisms responsible for microvascular dysfunction can be multiple and not necessarily the same in all patients. They may include (1) structural abnormalities, such as fibrosis and medial hyperthrophy50; (2) impaired endothelial and nonendothelial vasodilator function119; (3) enhanced constrictor response of smooth muscle cells, possibly involving increased membrane Na^+ -H^+ exchanger or intracellular rho-kinase activity120,121 and 122; (4) increased release of local vasoconstrictor autacoids (e.g., endothelin-1123,124 or angiotensin50); and (5) abnormal neural stimuli. Evidence of abnormal cardiac sympathetic function was documented by ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, which showed total absence of cardiac MIBG uptake in 42 percent of patients and regional defects, matching thallium perfusion

defects, in another 33 percent.125 (Fig. 46-9).

FIGURE 46-9 Typical cardiac scintigrams obtained 3 h after the injection of half a dose of ^{123}I-metaiodobenzylguanidine (MIBG) in a healthy subject (*left panel*) and the other half in a patient with syndrome X (*right panel*). Cardiac MIBG uptake was normal in the control subject and totally absent in the patient with syndrome X, in contrast with his normal lung and liver MIBG uptake. The total absence of cardiac MIBG uptake was confirmed in follow-up studies at 1 and 12 months, consistent with a persistent impairment of cardiac sympathetic function. (From Ianza et al.125 With permission.)

Acute Thrombosis

Intraluminal thrombi are the most common finding in patients with acute coronary syndromes. Most thrombi are composed of platelets and fibrin in variable proportions; they often develop at the site of non-flow-limiting coronary stenosis. Thrombosis may reduce or interrupt blood flow by itself or in combination with local or distal vasoconstriction (triggered by thromboxane, serotonin, and thrombin)126 (Fig. 46-10). Fresh thrombi may have a different fate, as they may grow to occlude the artery, lyse completely, or become organized and contribute to plaque growth.

FIGURE 46-10 Vicious cycles leading to the formation and growth of an occlusive coronary thrombus. An occlusive red thrombus can form rapidly, within minutes, at the site of a highly thrombogenic injury (for example, the rupture of a strongly thrombogenic plaque). An occlusive platelet thrombus can form gradually at the site of weak but very persistent thrombogenic stimuli (for example, a persisting inflammatory process). A mural thrombus resulting from a weakly thrombogenic plaque fissure or from a transient local inflammatory process may evolve into occlusive thrombosis only in the presence of prothrombotic states or of blood flow stasis induced by local or distal coronary constriction. The components of these vicious cycles and their gain may have variable importance and prevalence in different groups of patients. Prothrombotic states may result from any acquired or genetic alteration that leads to enhanced platelet reactivity or thrombin activity or to reduced fibrinolysis. (From Virdis et al.115 With permission.)

MECHANISMS OF ACUTE THROMBOSIS

Intracoronary thrombosis may result from strong or weak thrombogenic stimuli.126 *Strong thrombogenic stimuli* cause rapid thrombus growth with massive inclusion of red cells in the fibrin mesh (*red thrombi*), leading to persistent vessel occlusion within few minutes, as in the copper coil animal model. Strong thrombogenic stimuli may be represented by the mechanical rupture of a lipid-rich atherosclerotic plaque. *Weak thrombogenic stimuli* cause slow, progressive deposition of platelets and formation of platelet-fibrin thrombi (*white thrombi*, as in the electrical wire animal model). Weak thrombogenic stimuli may result from the fissure of plaques with low thrombogenic potential or from a local inflammatory activation of the vascular wall caused by infectious or noninfectious stimuli.44,127,128 and 129 Thrombus growth is determined mainly by the intensity, duration, and recurrence of the weak inflammatory stimuli.

The hypothesis that thrombosis may occur at the site of identifiable “vulnerable” coronary plaques is attractive and is currently stimulating the development of new research tools for their clinical

detection. However, morphologically or functionally vulnerable plaques may be potential sites of thrombosis because of mechanical rupture (as they have a large central lipid pool and a thin cap)130 or because they are the site of acute inflammatory processes,49 which cause endothelial activation and possibly also erosion and rupture. Plaque vulnerability may persist for days, weeks or months. Interestingly, in acute coronary syndromes, vascular inflammation131 may be associated with multiple fissured and complicated plaques throughout the coronary bed,132,133 and 134 and possibly also in remote vascular areas.135

The different mechanisms responsible for or contributing to coronary thrombosis and acute coronary occlusion may not have the same prevalence in different geographic, ethnic, age, and sex groups, yet they may influence the individual response to antiplatelet, antithrombotic, and acute reperfusion strategies.